(a) providing a composition comprising an entity which comprises at least one domain to a cell of interest, wherein said domain or domains are attached to a nucleic acid component which is in non-double stranded form and

(b) administering said composition in vivo or ex vivo.

305. (newly presented) A method of introducing a nucleic acid component into cells from an organism ex vivo comprising:

(a) obtaining cells of interest from said organisms;
(b) providing a composition comprising an entity which comprises at least one domain to a nucleic acid component;
(c) administering the composition of (b) into cells from an organism such that said composition is bound to said cells and
(d) readministering said cells back into said organism.

REMARKS

Claims 245-303 are pending in the above-referenced application. Claims 267, 268, 274, 284, 285, 286 and 302 have been amended to more distinctly claim that which Applicants regard as their invention and to advance prosecution. Claims 256, 269-271 and 288-289 have been cancelled. Applicants reserve the right to file subsequent continuation and/or divisional applications encompassing the subject matter encompassed by the claims originally presented. New claims 304 and 305 have been added to recite specific embodiments. The amended claims and new claims are supported by the specification.

Formal Drawings and a Supplemental Information Disclosure Statement will be submitted in a Supplemental Response.

The Rejections Under 35 U.S.C. 112, First Paragraph-Written Description

Claims 245-255 and 257-303 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action specifically states in the paragraph bridging pages 15 and 16:

> In response, although reduction to practice is not required, the MPEP as summarized above, does require for chemical compositions, that one of skill in the art be able to readily envision the claimed constructs, and that the specification provides a clear description of the structure and not just claim the structure by way of functional language. In the instant case, the claims are to constructs which have a certain function, but there is not a representative number of species of any such construct having the claimed functions in the specification as filed. The MPEP states that the identifying characteristics of the composition must be clear. In the instant case, the chemical structure is necessary to envisage the claimed compositions, and the specification has not described the chemical structure of the claimed nucleic acid compositions nor the antibodies nor other components of the compositions which have the claimed functions in a cell. The stick figures in the drawings do not adequately describe the chemical compositions claimed to the extent that one of skill in the art would be able to readily envisage the administration of the claimed constructs to a cell for producing a product.

It is further asserted in the Office Action that the Examples do not describe administration of the compounds of the present invention.

Applicants respectfully traverse the rejection. First, it is Applicants view that a representative number of species have been disclosed. As conceded in the Office Action on page 6, last paragraph

> The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 21-23.

In Applicants view, an adequate description of these species was provided in the specification as well as the figures. Applicants particularly take issue with the assertion made in the Office Action that the stick figures in the drawings do not adequately describe the chemical compositions. The MPEP in section §2163 II.A.3. (a) states:

> An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., *Vas-Cath,* 935 F. 2d at 1565 19 USPQ2d at 1118 ("drawing alone may provide a 'written description' of an invention as required by Sec. 112"); *In re Wolfensperger,* 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America v. United States*, 284 F.2d 391, 298, 155 USPQ 697, 703 (Ct. Cl. 1967) ("In those instances where a visual representation can flesh out words, drawings may be used in the same manner and with the same limitations as the specification,"); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("In claims

> involving chemical materials , generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.") The description need only describe in detail that which is new or not conventional. See *Hybritech v. Monoclonal Antibodies,* 802 F.2d at 1384, 231 USPQ at 94; *Fonar Corp. v. General Electric Co.*, 107 F.3d at 1549, 41 USPQ2d at 1805 (source code description not required). This is equally true whether the claimed invention is directed to a product or a process.

Figures 1-23 are sufficiently detailed and meet the criteria set forth in the MPEP. The stick figures presented in the figures were certainly standard for figures presented by those of ordinary skill of the art to describe a construct or composition. Certainly, sequences of these constructs are not necessary for the understanding of the principles illustrated in the procedures taught in the figures. To support Applicants' position, Applicants submit herewith as Exhibit A the following basic texts available at the time of the instant invention.

1. Davis et al., Basic Methods in Molecular Biology, Elsevier, New York, 1986;
2. Old et al., Principles of Gene Manipulation, Blackwell Scientific Publications, London, 1986;
3. Perbal, A Practical Guide to Molecular Cloning, John Wiley & Sons, New York, 1984;
4. Maniatis et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, 1982

Each of these references contain schematic diagrams for obtaining constructs and how they would function. The level of detail used in these references is very similar to that provided in the figures in the instant application.

Furthermore, Applicants take issue with the assertion made in the Office Action that it is necessary to provide the chemical structure of the claimed nucleic acid compositions, antibodies or other components of the compositions that have the claimed functions in a cell. This assertion is *contra* to the policies stated in the MPEP II.A.3.:

> Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art.

Applicants assert that sufficient identifying characteristics are provided regarding the components of the compositions of the present invention. The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49. Various examples of useful domains are described. Examples of various antibodies are provided in the paragraph bridging 53 and 54. These include useful domains with non-specific cell binding properties (see page 53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Furthermore, the specification in addition to the Examples does describe the following specific embodiments:

A. ATTACHMENT OF NUCLEIC ACID COMPONENTS TO MONFUNCTIONAL BINDERS

1) Covalent attachment of a nucleic acid component to a monofunctional binder which possess a domain to a cell (pages 59-61);

2) Specific non-covalent attachment of a nucleic acid component to a monofunctinal binder which possesses a domain to a cell (pages 61-62);

3) Non-specific non-covalent attachment of a nucleic acid component to a monofunctional binder which possesses a domain to a cell (page 62)

B. ATTACHMENT OF CELLS TO MONOFUNCTIONAL BINDERS WITH DOMAINS TO A NUCLEIC ACID COMPONENT

1) Covalent attachment of a cell to a monofunctional binder which possesses a domain to a nucleic acid component (pages 63-64);

2) Specific non-covalent attachment of a cell to a monofunctional binder which possesses a domain to a nucleic acid component (pages 64-65);

3) Non-specific non-covalent attachment of a cell to a monofunctional binder with a domain for a nucleic acid component (provides an example of a polylysine/anti-adenovirus antibody) (page 65);

C. BINDING OF CELLS TO NUCLEIC ACID COMPONENTS THROUGH BIFUNCTIONAL BINDER MEDIATION (pages 65 and 66)-discloses modifying an antibody to adenovirus by addition of a homopolymer such as poly T and modifying the Fab fragment of an antibody to a cell surface marker, such as CD4 with a homopolymer, such as poly A.

Applicants also note that *contra* to the assertions made in the Office Action, the specification actually does disclose that the compositions of the present invention may be administered either *in vivo* or *ex vivo*. The specification on page 13, lines 17-18 cites Yu et al., 1994, Gene Therapy 1:13-

26 which is incorporated by reference. Yu et al. actually discloses various methods for administering vectors into cells in culture as well as into whole organisms. A copy of Yu et al. is attached hereto as Exhibit B. Furthermore, as will be discussed in further detail below, methods for *in vivo* and *ex vivo* administration were well known in the art. Any methods currently in use could be used appropriately.

In view of the above arguments, Applicants assert that the rejection has been overcome. Applicants therefore request that the rejection under 35 U.S.C. 112, first paragraph (written description) be withdrawn.

The Rejections Under 35 U.S.C. 112, First Paragraph-Lack of Enablement

Claims 263-265, 281-283 and 299-301 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the Examiner's view, the specification while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*) does not reasonably provide enablement for the claimed methods of expressing a nucleic acid product in a whole organism (*in vivo*). It is further asserted in the Office Action in the paragraph bridging pages 22 and 23 that

> Although the instant claims 263-265, 281-283 and 299-301 do not specifically state that the nucleic acids in the claimed compositions are antisense nucleic acids, the specification as filed predominantly discusses use of the U1-anti-HIV constructs for administration to cells for antisense downregulation of HIV in the cells. Thus, the claims as written, which involve administration of these nucleic acid compounds to cells, including cells in a whole organism, have a high level of unpredictability in the art analogous to that in the antisense field. Furthermore, for the purposes of the instant rejection, *in vivo* below is

> considered to embrace both in vivo and *ex vivo* administration as claimed since *ex vivo* administration is also administration of the antisense and cells to a whole organism.

Applicants respectfully traverse the rejection. First, as noted above, the specification actually did incorporate by reference Yu et al., 1994, Gene Therapy 1:13-26 which actually discloses various methods for administering vectors into cells in culture as well as into whole organisms (Exhibit B). Secondly, methods were certainly well known at the time of the invention in the art for expressing a nucleic acid product in a whole organism. Examples of such teachings are attached hereto as Exhibit C:

1. Miller and Vile, 1995, "Targeted vectors for gene therapy", FASEB J 9:190-199;
2. Ally et al., 1995, "Prevention of autoimmune disease by retroviral-mediated gene therapy", J. Immunol. 155:5404-5408;
3. Lau et al., 1995, "Retroviral gene transfer into the intestinal epithelium", Hum. Gene Ther. 6:1145-1151

Applicants note that the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC 112, first paragraph. Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehlin v. Secher* 24 USPQ2d 1513, 1516 (BPAI 1992). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *U.S. v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Third, Applicants take issue with the assertion that administration of nucleic acid compounds to cells in a whole organism has a high level of unpredictability in the art analogous to that in the antisense field. The method of the present invention is directed to a method of delivery of the composition of the present invention not the

nucleic acid component itself. Furthermore, it is Applicants position that the administration of nucleic acid products in the sense or antisense orientation would not be unpredictable. Applicants submit as Exhibit D, the following references showing the correlation between *in vivo* and *in vitro* results using both ribozyme, RNAi sequences and vectors containing sense and antisense sequences:

1. Opalinska and Gewirtz, 2002, "Nucleic-acid Therapeutics: Basic Principles and Recent Applications", Nature Reviews, Drug Discovery 1:503-514;
2. Voorhoeve and Agami, 2003, "Knockdown Stands Up", Trends in Biotechnology 21:2-4;
3. Vacek et al., 2003, "Antisense-mediated redirection of mRNA splicing", Cell. Mol. Life Sci. 60:825-833,
4. Kelley et al., 2003, :"CaSm antisense gene therapy: a novel approach for the treatment of pancreatic cancer", Anticancer Res. 23:2007-13;
5. Xu et al., 2003, "Molecular Therapeutics of HBV", Current Gene Therapy 3: 341-355.

These references also show that administration of nucleic acid compounds to a whole organism is accepted and that there is an accepted level of predictability with respect to these methods.

In view of the above arguments, Applicants assert that the rejection has been overcome. Applicants therefore request that the rejection under 35 U.S.C. 112, first paragraph (enablement) be withdrawn.

The Rejections Under 35 U.S.C. 102(e)

Claims 247-248, 250-255, 257-259, 262-263, 266-268, 270-281, 284-286, 288-299 and 303 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer

et al (US Patent 5,574,142). The Office Action specifically states with respect to claim 247:

> Claim 247 is drawn to a composition comprising (a) a non-natural entity which comprises: at least one domain to a specific nucleic acid component; and at least one domain to a cell of interest; an (b) said specific nucleic acid components; wherein the domain or domains said nucleic acid component are different from the domain or domains to said cell.
>
> Meyer et al. taught in figure 2 that an antisense oligonucleotide (ODN) which is specific to a nucleic acid of interest inside a cell, is attached via a cleavable peptide to a polymer carrier that is a domain that is recognized by a ASGP receptor on the surface of a liver cell.

However, the examiner did consider claims 245, 246, 260, 261, 264, 265, 269, 282, 283, 287, 300 and 301 to be free of prior art. The Office Action specifically states

> Meyer et al., did not teach that the ODN construct having at least one terminus comprising a polynucleotide tail was hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand nor where the binder and the domain are the same (claims 249, 269 and 287); the prior art did not further teach in vivo and ex vivo use of the construct of Meyer et al. (claims 261, 264, 265, 282, 283, 300 and 301).

Applicants respectfully traverse the rejection. The composition of Claim 247 comprises:

> (a) a non-natural entity which comprises:
>
> at least one domain to a specific nucleic acid component; and at least one domain to a cell of interest; and
>
> (b) said specific nucleic acid component;

> wherein the domain or domains to said nucleic acid component are different from the domain or domains to said cell.

In contrast, Figure 2 of Meyer comprises a non-natural entity comprising a polymer carrier that is a domain that is recognized by a ASGP receptor on the surface of a liver cell. The polymer carrier is attached to a cleavable peptide. The cleavable peptide is attached to an oligonucleotide antisense sequence. The antisense sequence binds to a nucleic acid sequence inside a cell. Therefore the polymer carrier attached to a cleavable peptide could be considered to be the domain to a cell of interest and the antisense sequence could be considered to be the domain to the nucleic acid component in the cell. As shown in Figure 2 of Meyer et al., the entity in the lysosome of the cell contains a domain to a cell of interest and a domain to a nucleic acid component but **not** the nucleic acid component itself. The entity of Meyer et al. in the nucleus of Meyer et al. comprises a domain to a nucleic acid component as well as the specific nucleic acid component but not longer comprises a domain to a cell of interest. In short, Meyer **does not** contain all three elements in a single composition. Therefore, claim 247 and claims 248-255 and 257-266 which depend from claim 247 are not anticipated by Meyer et al.

Applicants further note that as suggested in the Office Action, claims 267 and 285 have been amended to advance prosecution and recite that the entity also contains a binder and that the binder and domain are the same. Applicants do reserve the right to file subsequent continuation and/or divisional applications on the subject matter in the cancelled claims. Furthermore, new claims 304 and 305 have been added to recite specific embodiments. It is Applicants view that these new claims are free of the prior art.

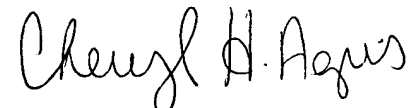
In view of the above arguments, claim amendments and new claims, Applicants assert that the rejections under 35 U.S.C. 102(e) have been overcome. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. 102(e) be withdrawn.

Summary and Conclusions

Claims 245-302 are presented for further examination. Claims 267, 268, 274, 284, 285, 286 and 302 have been amended. Claims 256, 269-271 and 288-289 have been cancelled. New claims 304 and 305 have been added.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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